I N S P I R E D  B Y  S A L K

The Salk Institute as a beneficiary of our trust was the result of a two-part process. First, my wife and I came to understand the purpose and benefits of a Charitable Remainder Trust (CRT). Then we had the opportunity of selecting the beneficiaries. We decided to each select an organization dedicated to improving the basic quality of life. I chose the Salk Institute with surprisingly little effort.

Jonas Salk, as well as the Institute, have been recurring interests for me. I recall asking lots of questions about getting my polio vaccine before entering school in Ohio. That is when I first remember hearing about Jonas Salk and how vaccines work. Later, during elementary school, our weekly science paper covered the Salk Institute and its distinctive buildings. During my graduation year from college, I came to San Diego for a job interview and my cousin took me to the Salk Institute. We walked around to enjoy the buildings and the view. I had forgotten it was here.

Around 1996, I read an interview in The San Diego Union-Tribune, where I learned much more about the workings of the Salk Institute and its funding. Until that point I had no idea how the Institute operated. A year or so later, we set up our CRT. The recent memory of the article and my high regard for the organization convinced me what my choice should be.

Mario M. Scipione
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DURING THE PAST YEAR, the world of biomedical science has been altered forever with the solving of the human genome. We have entered a new age of discovery, a post-genomic era in which scientists will probe ever more deeply into the unsolved mysteries of biology. The result will be a better understanding of disease leading to new medical treatments and cures.

This issue of Salk Signals provides a brief look at how Salk scientists will be exploiting post-genomic science in the future. We will establish a new research group in chemical biology and proteomics, sciences aimed at understanding the structure and interactions of proteins and creating new molecules to probe protein function. We will focus efforts on stem cells, which are key to providing new ways to regenerate or replace diseased tissues. Our regulatory biologists will study how genes are turned on and off in normal and diseased cells. And our computational and theoretical biologists will use computer simulations to interpret data and to establish hypotheses that can be tested in the laboratory. These new research initiatives will require the hiring of a new generation of Salk scientists who will conduct independent research studies as well as carry out collaborative research with faculty in different fields, which has been a hallmark of the Salk’s success.

As part of this effort, the Institute welcomed two new scientists this year. Roland P. Riek joined the Institute as an assistant professor in structural biology and director of the new NMR (nuclear magnetic resonance) facility, which will help us determine the structure and dynamics of proteins and their interactions. Dr. Riek will use NMR spectroscopy to continue his studies of prion proteins, which are infectious and transmissible, and have been identified as the cause of mad cow disease and Creutzfeldt-Jakob disease in humans. Jan Karlseder also joined the faculty during the past year as an assistant professor in the regulatory biology laboratory. Dr. Karlseder studies cell replication, particularly the role and regulation of telomeres, which are located at the end of chromosomes. One of his goals is to understand the molecular mechanisms that result in telomere shortening, a natural process that occurs with aging. Cells with critically short telomeres enter a period of arrest called senescence, which is believed to be a potent tumor suppressive mechanism.

Also included in this edition of Salk Signals is a special Annual Report section and our Honor Roll of Donors. For fiscal year 2001, more than 900 individuals, families, corporations, foundations and groups donated more than $35 million to support Salk’s activities. We are especially grateful to the March of Dimes, which provided the initial funding for the Salk Institute and which has graciously supported our scientific pursuits throughout the years.

I would also like to thank the members of our Board of Trustees for their guidance, support and financial backing. In addition to giving of their resources and talents, the trustees and many other supporters have donated their time to the Institute in various capacities. We are indebted to all of you.

RICHARD A. MURPHY
PRESIDENT AND CHIEF EXECUTIVE OFFICER
FROM THE JOURNALS

Link between Breast Cancer Drug and Heart Failure

The probable link between the breast cancer drug Herceptin and cardiac failure, one of its common side effects, was identified by a team led by Associate Professor Kuo-Fen Lee and reported in the May 1 issue of the Journal of the American Medical Association.

Herceptin targets a protein called Her2, which is found in excess in some breast cancer cells. The study shows that the mouse version of Her2 (called erbB2) is needed for proper heart function.

"It was possible that Herceptin triggered cardiac malfunction by a number of mechanisms," said Lee, "and now it appears that the drug's anti-cancer mechanism, particularly cardiomyocyte contraction, is directly related to the drug's anti-cancer mechanism, it should be possible to design strategies to counteract the dangerous side effect.

"If we could develop agents that can stimulate the heart, particularly cardiomyocyte contraction, then those might allow you to use Herceptin aggressively while protecting the heart," said Lee. Efforts in his laboratory are focusing on this approach.

New View of Brain May Shed Light on Autism

According to generally accepted neuroscience dogma, the brain works somewhat like an electronic bucket brigade, with incoming signals passed from one region to the next in a linear fashion.

This somewhat passive role is challenged by a recent study led by Salk Professor Terrence J. Sejnowski and his team in the Computational Neurobiology Laboratory. Instead of the bucket brigade metaphor, these scientists see the brain more as a symphony orchestra waiting to come into harmony with the lifting of a conductor's baton.

"Our data indicate the brain 'at rest' is more like a symphony orchestra warming up — one hears a lot of discordant activity," said Sejnowski, referring to the study, which appeared in the Jan. 25 issue of the journal Science.

"Then the conductor — or stimulus — appears on the scene and imposes synchrony."

In the recent work, the investigators applied a mathematical technique called ICA (Independent Component Analysis) that allowed them to examine each of more than 13,000 experimental trials individually.

The result, a generation of strong waves as depicted on an electro encephalogram (EEG) recording, suggests a far more dynamic view of the brain's activity.

It also opens new avenues to explore certain brain dysfunctions, including schizophrenia and autism. Neuroscientists know that some important brain responses are too small or missing in autism. The new method of analysis may help to explain the underlying biological reasons for the altered responses.

One possibility relates to the symphony metaphor; coherence may be missing in autistic individuals. In other words, there is no conductor, and therefore no reorganization. Each instrument continues to play its own tune. New approaches to therapies might focus on restoring harmony.

Genes and Cancer

Genetic instability is a distinguishing feature of cancer cells. Extra copies of certain growth-promoting genes, as well as broken or rearranged chromosomes accumulate in cancer cells, while other genes — usually those that rein in growth — are missing. This genetic turmoil fosters the aggressive and unchecked growth and division of cancer cells.

Recent work from Salk Professor Geoffrey M. Wahl and his group in the Gene Expression Laboratory points toward one cause of this instability. In a recent paper, published in the research journal Molecular Cell, the investigators show that mutations in a gene called c-myc can create DNA damage. They also show that over-stimulation of the c-myc gene can shut down the mechanisms a cell normally uses to monitor and check genetic damage. Specifically, c-myc can depress the activity of a protein known as p53, an important "guardian" of a cell's genetic integrity.
Senyon Choe, a structural biologist, searches his mind for a metaphor to best place the life sciences in a historical context: where we’ve been — the era of the gene — and where we’re going — the era of the protein. He turns to music. By analogy, Choe says, the gene is like a musical score, with all the notes and timescales carefully charted for each instrument. By extension, proteins — the products encoded by genes — are akin to the violinist or piano player who carries out the instructions set down by the score.
Now, here’s where it gets complex.

“There’s only one music score, but there are many different ways of playing the same music,” says Choe, an associate professor at the Salk Institute. “Consider the way a little child plays and the way (Vladimir) Horowitz plays a Beethoven piece.

“So the complexity of protein function and regulation is far greater than the complexity of genetic makeup.”

Consider the scope of the problem. Briefly, there are far more proteins than the approximate 30,000 genes identified by the Human Genome Project, perhaps 10 to 100 times as many. To truly understand how these proteins work together in concert, scientists must determine how ensembles of proteins come together. Only then, will scientists truly understand how the body functions and what goes wrong in disease.

This is the promise of proteomics, the technical expression for the study of proteins and their interactions. If all works, researchers like Choe envision a new era in medicine, where drugs and other therapies can be customized for each individual patient. But don’t discard the tubes and bottles in your medicine cabinet just yet.

“We thought when we knew the genome, we would know everything we needed to know,” said Noel, “how these proteins change as the cell grows, divides, differentiates within tissues, ages and dies.

“We want to know how each component and each complex changes as a function of all these events.”

Much of this work is being driven by technical advances that are allowing scientists to see proteins as never before — from the minute grooves, ridges and pockets that make up their three-dimensional structures to their interactions with other proteins, no matter how fleeting.

This list includes mass spectrometry, which, by sorting and identifying molecules based on their mass, helps scientists to identify proteins in functioning networks. Then, there’s nuclear magnetic resonance (NMR), which produces clear images of proteins as they merge, trigger intricate chemical changes, and then part. These technologies, combined with genetics and x-ray crystallography — which produces brief snapshots of proteins — are expected to generate far more accurate models of proteins at work.

With such sophisticated techniques, Noel hopes to gain a better understanding of plant evolution to
To truly understand how these proteins work together in concert, scientists must then determine how ensembles of proteins come together. Only then, will scientists truly understand how the body functions, and what goes wrong in disease.

find out how and why plants produce the 100,000 or more different proteins during their life cycles. Some of these molecules are harmful to humans when ingested; others provide valuable nutrients. And a few other proteins and molecules hold the potential to cure disease, including heart disease and cancer.

So, aside from answering fundamental questions about the chemistry of plant proteins, Noel says this research one day could yield crops that help prevent or treat life-threatening ailments.

“By enhancing food stuffs for the production of beneficial molecules we can ingest easily and cheaply,” he says, “we can produce something that’s quite beneficial to mankind.”

Before plants like these can be engineered, Noel and others are working to identify key protein networks responsible for health benefits. From these, he hopes to create dynamic models of how they perform the biological task in question. For the most part, these protein-protein interactions are weak and fleeting.

“With traditional analytical tools, people have studied protein-protein interactions that typically bind strongly with each other,” said Noel. “That is, they come together and they rarely, if ever, come apart — such as an antigen-antibody interaction. Those are easy to study.

“But such interactions are rare, and there’s a whole host of protein-protein interactions that are relatively weak and highly regulated, which form and dissolve over time.

“As a general theme, the real goal of the next decade will be to understand the nature of these weak interactions, with the aid of advanced technology.”

For his part, Senyon Choe believes “protein chips” — the counterparts to the much-publicized “gene chips” — will help scientists to better identify proteins, their functions and what goes awry to cause disease.

Choe is a member of the national Joint Center for Structural Genomics, which has as its goal to determine the three-dimensional structures of up to 2,000 proteins, using “high-throughput technology” that includes robotics and massive computational resources.

As part of this effort, he is working with scientists at University of California, San Diego, Stanford and the Scripps Research Institute to build a chip of about a dozen proteins that mimics the activity of TGF-beta receptors, a class of proteins that is essential for a wide variety of functions. These include cell growth and differentiation, tissue repair and bone formation, immune response and tumor formation, and programmed cell death.

“We’d like to use this small set of proteins as a ruler, so to speak, to mirror how this receptor works in the body,” said Choe. “It can be used as a tool to determine developmental stages, how signals are transmitted from cell to cell. We can also use this chip to assess the status of disease, including cancer, so we can test the effectiveness of a particular anti-cancer drug on tumor growth.”

Such discoveries offer just a glimpse into what’s possible.

Choe returns to the music metaphor. “It’s like we’ve just discovered the entire score of an old Beethoven piano concerto,” he says. “To play it, we call upon the components, those individual proteins. With proteomics, we’re going to learn how to understand who those players are and then how they come together to play it.

“With that knowledge, we can gain a better understanding of life itself. And then we’ll get the individualized medicine we’re seeking. It will happen. I have no doubt. It’s not hype. But it will take time.” –By Warren Froelich

To truly understand how these proteins work together in concert, scientists must then determine how ensembles of proteins come together. Only then, will scientists truly understand how the body functions, and what goes wrong in disease.
It's like no other infectious agent. Unlike bacteria, viruses or any other known pathogen, this strange particle has no genetic material. It's pure protein.

During the past couple of years, however, this entity called a prion has gained international notoriety for another reason: it's been implicated as the culprit responsible for bovine spongiform encephalopathy (BSE), commonly called mad cow disease.

Though thousands of cattle in England and other parts of Europe have been destroyed to help prevent the spread of this neurodegenerative disease, health officials and others worry about the potential impact on the hundreds of thousands of humans who consumed infected beef over the past decade.

“It’s in our interests to move as fast as we can to find out more about prion proteins,” said Roland P. Riek, a structural biologist who joined the Salk Institute last year from the Swiss Federal Institute of Technology in Zurich, Switzerland.

“But it’s fundamental science, and it’s going to take a huge amount of time to find anything that might lead to a drug or anything like that,” he added.

To find weapons against this public health menace, Riek has enlisted the support of sophisticated nuclear magnetic resonance (NMR) instruments to get a better view of its structure and, potentially, how it causes infection in the brain. Just as astronomers tune into radio waves emitted by objects in outer space, NMR works by tuning into the radio waves emitted by atoms within materials.

“I think the important thing with...
NMR is that we are able to get a better glimpse of protein-protein interactions,” said Riek, who directs Salk’s new NMR facility, “and we are able to work in solutions in environments that are physiologically similar to living systems.”

The term prion (for proteinaceous infectious particle) was first coined in 1982 by University of California, San Francisco scientist Stanley Prusiner. It was also Prusiner who proposed the heretical notion that prions cause a variety of brain disorders, including Creutzfeldt-Jakob disease in humans, when a benign form of the protein — typically found at the surface of normal cells — becomes distorted. This abnormal prion protein, he said, then binds with other normal proteins, which then become distorted, producing a chain reaction that ultimately results in the widespread death of brain cells.

Using NMR facilities in Zurich, in 1996 Riek and colleagues unveiled the first three-dimensional view of a normal prion particle. The rather unusual protein consists of two distinctly different segments of approximately equal size: half appearing as a sphere-like object, the other half forming a long, flexible tail.

From the structure, Riek and other scientists are gaining early clues into normal prion protein activity, and what might happen when the protein turns infectious.

Among other things, Riek has found small structural differences across several species. Such insights might provide critical information about whether prions from one species, such as cows, can infect another species, including humans.

To continue this work, Riek will rely on a new NMR instrument housed at the Salk Institute. The centerpiece of the instrument is a large core magnet that generates an alignment of nuclear magnets called spins, which then are manipulated by radio waves.

Riek will be collaborating with Salk scientists investigating a variety of structures important for understanding myriad ailments, including AIDS, mental disorders and cancer.

“San Diego is an incredible center for NMR work,” said Riek. “At Salk, we’re coming together real fast with several collaborations already.

“This synergy of activity should give us information about binding interfaces, about structural details, and about enzymes that could result in the rational design of new drugs. That’s the goal.”–By Warren Froelich
Professor Walter Eckhart may present a calm and cool veneer, but words like “exciting, challenging, unparalleled” pepper his speech about the new era of post-genomic discovery.

“It’s a particularly exciting time to be working in biology and to see how all this basic knowledge is able to be applied to important human problems,” said Eckhart, a professor in the Molecular and Cell Biology Laboratory and director of the National Cancer Institute-designated Cancer Center at the Salk Institute, one of only eight in the country.
The completion of many genomes, including the much-heralded Human Genome Project, has cracked open the door to new realms of discovery in basic biology, and researchers like Eckhart are pushing it ever wider with their considerable intellect and new technologies. If human beings have only twice as many genes as a worm, then what distinguishes humanity?

“It’s a revolution in biology,” said Fred H. Gage, a professor in the Laboratory of Genetics and an expert on stem cells. “And one that will have profound effects on how we do science, as well as on how we think about human health and disease.”

**Painting a complete picture**

“We are getting quite a lot of information about the components of cells, for example the genes and the machinery that make up proteins, and the components of how cells communicate,” said Eckhart.

“But that is only a partial picture of how cells work. Cells are more than just a mixture of their components. If you put all of the components in a bag and shook them up, you wouldn’t get a cell.”

So what would paint a more complete picture — one that would lead to an understanding of the “important human problems” of disease?

Learning how these components work together to create a functioning whole, explained Eckhart.

For example, the mechanics of mitosis (the process by which the body produces new cells) have been observed and studied for decades, but scientists don’t know much about the molecular means by which chromosomes (which contain genetic material) are duplicated and partitioned into daughter cells in an accurate way.

“Understanding this process better is tremendously important for grasping the complexities of diseases such as cancer,” said Eckhart, “where there is genetic instability and a lot of chromosomal rearrangements and changes. And the recent accumulation of information about genes and how they function will help us to comprehend this process, as well as many other cellular processes.”

Now that DNA microarrays, or gene chips, allow researchers to examine the activities and relationships of large groups of genes, they can determine evolutionary connections between simple organisms and more complex ones.

“We can study the relationship of genes from one organism to another much more easily as a result of the various genome projects — the viruses, the fruit fly, bacteria and so on,” said Eckhart. “We are beginning to see that by understanding the development and structure of simple organisms, we can understand them in complicated organisms. So we study fruit flies and other simple organisms to get an idea of how similar processes work in complex organisms, such as chickens, mice and humans.”

Such knowledge could lead to more rapid and precise diagnosis of disease, determination of who might be more susceptible to certain diseases, and the development of novel therapies.

As the new era moves forward, Eckhart envisions several specific
overarching goals: understanding embryonic development, how the functions of the body are coordinated and stem cell biology.

UNDERSTANDING STEM CELLS
According to Gage, the Human Genome Project has changed the way researchers look at stem cells — cells that have the ability to divide and give rise to specialized mature cells for all organs of the body, such as the liver, brain and blood.

“Because the human genome is available, we can use that knowledge to determine what genes are unique for embryonic versus adult stem cells,” said Gage, leaning forward over his desk to emphasize his point.

“We can also identify genes that are unique to stem cells versus more differentiated cells, such as liver cells or neurons. In addition, we can determine the difference between normal and diseased cells.”

What Gage anticipates will keep him and his colleagues “busy for a long period of time into the future” is how to obtain the most primitive embryonic stem cell lines (those that can give rise to most tissues), how lineage restricted stem cells (more specialized stem cells that give rise to cells with a specific function) can shift and how organs take shape.

Creating new embryonic stem cell lines through what is popularly known as “therapeutic cloning,” or as Gage prefers to call it, “nuclear transfer,” could lead to tailoring stem cells for the individual to avoid tissue rejection. In nuclear transfer, the nucleus is removed from an unfertilized egg, and DNA from an adult cell is inserted into this egg. When the “new” egg grows into a few hundred cells, stem cells can be harvested that would match the adult donor’s genome.

“Nuclear transfer — understanding what is called the reprogramming of the genome so we can take cells and teach them how to become more primitive, to again recapitulate the embryonic stem cell lineage — is a very exciting issue,” said Gage. His mind leaps ahead to a future that involves discovering if a stem cell can convert from one lineage to another. Can stem cells targeted to become blood cells or liver cells turn into muscle or brain tissue?

“There is a tremendous amount of information that needs to be gathered now,” Gage emphasized, before moving on to discuss his next anticipated venture — organogenesis.

“It is one thing to say you have a stem cell that can make all these different individual cells. It is another to say that you can take a stem cell and make a heart, liver or any other organ. And that is what organogenesis is all about.”

A brain, for instance, is not composed of one type of stem cell, but myriad stem cell lines — a mixture from blood, nerves, muscle. To create an organ as complex as the brain or the heart, scientists have to look at the interaction of all the different stem cell lineages and how they coordinate in time and space to give rise to a functioning organ.

“For a basic scientist, that is just exciting. How does that happen? And of course, the practical implications are tremendous. There is the possibility that we could reconstruct an organ in a dish that can be used for transplantation,” said Gage.

“It sounds a little bit out of the realm of science fiction, but I don’t think it is impossible.”

Indeed, these kinds of questions are those that researchers at the Salk Institute thrive on answering. “This is basic research,” said Gage. “These kinds of questions have important biological significance, but also have important practical implications as well.”

As for Eckhart, he always keeps in mind “that even though we are having fun doing this, what is important is that we are trying to alleviate human suffering.” –By Shannon Rose

As one cell divides to form two, its genetic material is first duplicated, then evenly separated into the two new cells. Mistakes in this process can lead to cancers or birth defects.
Tat (transactivating transcription factor) is like the engine of a train — without it, HIV-1 goes nowhere, which is exactly where biochemist Katherine A. Jones wants it to go. Jones, a Salk Institute professor in the Regulatory Biology Laboratory, has been studying the elusive machinations of the protein Tat for 18 years, since her postdoctoral days at the University of California, Berkeley, and the start of her career at the Salk Institute in 1986. And with an estimated 40 million people worldwide living with HIV or AIDS at the end of 2001, she is not about to stop anytime soon.

“AIDS is a major, major problem in the world today,” said Jones. The U.S. Census Bureau estimates that by 2010, the average life expectancy will be reduced by 40 years in Zimbabwe and Botswana, and in South Africa by 30 years.

“This is horrifying — the resulting population will be unlike anything we’ve ever seen before,” said Jones. “We hope our work here at the Salk Institute will help to stop these types of statistics in their tracks.”

Tat is essential for replication of the HIV-1 virus, which depends upon the proteins and machinery found in normal cells to duplicate itself. Once the virus has managed to replicate, it converts the host normal cell into a machine that spits out more and more copies of the virus, which are then released and find other cells to infect.

Jones and her team found that Tat, the first protein the virus makes once it infects a cell, binds with a protein complex already present in a normal cell — cyclin T1, identified by Jones during her tenure at Salk, and its partner, cdk9, a kinase. A kinase is a protein that adds a phosphate to other proteins in a cell in a process called phosphorylation.

Evidently, Tat serves as the engine, pulling the box cars, cyclin T1 and cdk9, to a different location in the host cell where the process of replication can begin. The lab is homing in on exactly how Tat moves the complex and thus turns it into a lethal combination.

“We are looking at the idea that Tat may be changing how the complex phosphorylates,” explained Jones.

“And that this phosphorylation is a requirement before anything can happen to start the whole process of activation and replication.”

She and her team hope that a further understanding of this crucial step for replication of the HIV-1 virus will lead to new treatments and therapies to block the Tat/cyclinT1/cdk9 partnership.

Cutting-edge technology at the Institute may help in her quest. She hopes to utilize the newly installed nuclear magnetic resonance (NMR) instrument to determine the structure of the cyclin T1/cdk9 complex.

“Once we can physically see the structural interactions we will have a better sense of how easy or difficult it may be to disrupt the recruitment of this complex by Tat,” said Jones.

“It clearly is a kinase that is widely used by the cell for regulation of many, many different genes — if not for all genes. So clearly, blocking all of the activity of the complex with a drug would not be ideal, but there is a window where an inhibitor could be administered at levels below that of harming its normal necessary functions.” –By Shannon Rose
The scene unfolding on Salk scientist Thomas M. Bartol’s computer makes one feel like an astronaut hurtling through a rainbow-hued asteroid storm. Odd forms and shapes whiz, whirl and occasionally collide. But it’s not a futuristic flight simulator that has Bartol’s attention. It’s a laboratory-generated simulation of a nerve cell “firing” and passing a message to another cell — an event that transpires a hundred million billion times a day in the brain as we go about the business of living.

The complexity of the human brain is staggering. A pinch of brain tissue the size of a grain of rice contains approximately a million cells, and each one of those can “talk” to 10 thousand other cells.
Bartol explains how he and his colleagues used a model to help settle one dispute about how neurons communicate with a particular muscle that moves the jaw.

“The connections between neurons and the muscles they innervate are called synapses,” he said. “All psychoactive drugs — both prescription drugs like Prozac and illicit or recreational drugs — act on synapses. So understanding synapses is essential to understanding brain function.”

On one side of the gap between a nerve and a muscle, the neurons contain many tiny vesicles, little sacks of molecules called neurotransmitters. When a neuron fires, it releases these transmitters into the gap between it and the muscle cell.

On Bartol’s screen, the transmitters resemble snowflakes, confetti — or asteroids, depending on the speed of the movie. Ultimately, they reach the muscle, where they dock with another specialized molecule called a receptor.

“After the receptor has bound two molecules of transmitter, the receptor...
changes shape — and we see it turn color,” explained Bartol. “The shape change is what permits electrical current to flow through the muscle cell and the muscle to contract.”

For many years, scientists had observed that responses on the muscle end were not uniform across the synapse. More receptors were activated in some areas than in other areas.

Many had puzzled over the reasons for this and carried out large numbers of experiments, none successful. Most were designed to test the theory that more transmitter was released at certain sites, thereby reaching the muscle more strongly on the opposing side of the gap.

“If you were looking at a river bank and found heaps of leaves accumulating at certain locations,” said Bartol, “in the simplest case, you might think there were a large number of trees shedding on the opposite bank.

“But it’s also possible that some underlying terrain or currents might be causing the pile-ups.”

Bartol and his colleagues were able to apply their model to show that the topography of the synapse could indeed account for the differences in receptor activation, even when the number of transmitter molecules released was the same at each location.

“Hundreds of experiments had been done to address the issue, but without resolution,” he said. “We hope in the future to be able to save experimentalists a lot of time by using models to rule out certain theories or point toward more likely ones.”

UNRAVELING HOW NEURONS WORK TOGETHER

Computational biologists also plan to scale up their modeling capabilities to examine large networks of synapses or neurons. This effort will be needed to understand the intricate and coordinated processes that underlie complex brain functions such as learning, memory and perception. Investigators on the Salk’s vision research team rely on modeling to help them unravel how hundreds of thousands of individual neurons work together to perceive the world. This work may lead to a new understanding of mental disorders such as schizophrenia, as well as visual prosthetic devices that could restore sight to those blinded by stroke.

And, ideally, investigators wish to understand the many other types of cells in the body, which could lead to new treatments for cancer, heart disease and a host of immune disorders such as arthritis.

“Building models requires not only biologists, but mathematicians, physicists and computer programmers as well,” said Sejnowski, who was trained as a theoretical physicist at Princeton.

“One of the hottest new areas of research is computational biology, at the intersection between computer science and biology. The next generation of students who will be doing experiments that involve looking at the entire genome and proteome will need to be as adept with using computer models as they are with carrying out experiments.” –By Suzanne Clancy

Computer-generated models of “messenger” molecules traveling from nerve to muscle.
Assistant Professor John H. Reynolds is working to understand visual perception. His work could provide insight into such disorders as schizophrenia, attention deficit disorder and autism.

For most of us, gazing through a kaleidoscope or glancing in a fun house mirror is an amusing diversion. But suppose you were forced to view the world permanently in a disorganized or distorted fashion?

Such is the plight of those affected by perceptual disorders. Individuals with Balint’s syndrome, for example, look out at the world around them in the fractured manner produced by kaleidoscopes. Those suffering from visual prosopagnosia cannot distinguish one person’s face from another’s.

“These conditions are extremely debilitating, as you can imagine,” said Salk Assistant Professor John H. Reynolds, the newest faculty recruit in the Systems Neurobiology Laboratory.

“They make it pretty much impossible to function normally.”

And like more common perceptual disorders such as dyslexia, the problems appear to lie not in the eyes, but in the brains of these individuals — particularly in how their brains process visual information.

“We really know very little about how objects are represented in the brain,” said Reynolds. Since joining the Salk Institute in 2000, Reynolds and his growing laboratory have been setting up tests designed to probe ideas about how the human brain recognizes objects and focuses attention. They hope that understanding the molecular and cellular bases of these brain functions will aid the design of therapies for perceptual disorders.
Reynolds finds modeling — using mathematics or computers to simulate the brain’s workings — to be especially important to his research progress.

“My own taste has tended toward simple models that give you alternatives that can be tested in straightforward experiments,” he said. Using this approach, his team recently uncovered a basic mechanism that appears to govern how we focus attention at the level of individual brain cells.

It turns out that when we pay attention to a particular location in space, our brains can detect things that would otherwise be invisible. That is, a spot in the lower right corner of a page might be too dim for us to notice if we are concentrating on the upper left corner. But once we turn our attention to the lower right, the spot becomes visible.

“Many competing theories existed about this phenomenon,” said Reynolds. “Earlier work had pointed to the importance of precise timing. With our collaborators at the National Institutes of Health, we were able to show that when an animal focuses attention on an area, the brain cells responsible for that area become synchronized. They begin to fire in unison, and this makes the signal they send stand out, like coordinated clapping in a stadium.”

Reynolds and his group hope that this new understanding may lead toward ways to cope with disorders such as autism and attention deficit disorder, which are characterized by problems with focusing or shifting attention.

But, in order to gain a more complete understanding of the brain, researchers will need to learn how cells in many brain areas work together. The presence of a leading team of computational biologists was a key factor in attracting Reynolds to take a position at the Salk Institute.

“Terry [Sejnowski] was definitely a draw,” he said. “His lab can build models that are biophysically realistic, involving different cell types, different patterns of connections.

“Modeling doesn’t necessarily give you the truth,” he added. “But it can help you eliminate ideas you might have thought were true, so we can avoid wasting our time on dead ends.” —By Suzanne Clancy
Thanks to Frederick B. Rentschler

Everyone associated with Salk owes a tremendous debt of gratitude to Frederick B. Rentschler for his many years of service and dedication to the Institute. Rentschler will step down as chair to become co-vice chair. Rentschler brought to the Salk extensive leadership experience from the corporate world, having served as the former president and chief executive officer of the Beatrice Companies, as well as executive vice president of BCI Holdings Corporation. He was a captain in the U.S. Marine Corps in the 60s and served as deputy director of the White House Fellows Program in the 70s.

Rentschler joined Salk’s board of trustees in 1988 and became chairman of the board in November 1995. During his tenure as chair, the Institute completed a 25,000-square-foot specialized research facility. Rentschler also created an endowed chair for young and promising scientists at the Institute. Perhaps most importantly, he presided over the planning for the Institute’s future success, which reviewed how Salk got to where it is today and what the Institute needs to build for tomorrow’s challenges.

When asked to assume everyday leadership of the Institute in 1999, Rentschler became Salk’s chief executive officer, serving until October 2000. Few have contributed so much of their time, talent and resources. For all three, the Salk Institute is deeply grateful.

Appointments

Two new trustees were appointed to the Salk board during its New York meeting in April. They are:

- Howard H. Newman, vice chairman and partner of New York-based Warburg Pincus LLC, a partner-owned investment firm with holdings in more than 180 companies in North and South America, Asia and Europe.

  Newman has been employed in several roles by Warburg Pincus since 1984, including managing director, vice president and associate. From 1974 to 1983, he held various positions with Morgan Stanley & Co., Inc. He serves as a director for several public companies, including ADVO, Inc.; Dime Bancorp, Inc.; Encore Acquisition Company; Spinnaker Exploration, Inc.; Cox Insurance Holdings, Plc.; EEX Corporation; and Newfield Exploration Company. He also is vice chairman of the Yale Alumni Fund.

  Newman earned bachelor’s and master’s degrees in economics from Yale and a Ph.D. in business-economics from Harvard University. He also was a Marshall Scholar in economics research at Cambridge University.
Darlene Marcos Shiley, a well-known San Diego philanthropist. Many San Diego organizations are the beneficiaries of the time and support provided by Shiley and her husband, Donald. These include the Shiley Eye Center at UCSD, the Shiley Sports and Health Center at Scripps Clinic, and the Shiley Theater at the University of San Diego (USD), in addition to KPBS-TV, the Old Globe Theater, and grants to the Salk Institute and UCSD for Alzheimer’s research. The Shileys have endowed scholarships and fellowships at several institutions.

Shiley also has served on the board of ScrippsHealth, is a longtime member of the USD Board of Trustees, and has been active with the UCSD Board of Overseers and the KPBS Community Advisory Board. She was elected to the Downtown Project Area Committee and appointed by the mayor to the Commission for Arts and Culture.

A former television promotion/public relations director, she is the recipient of many honors and awards, including the San Diego Press Club Community Activist-Headliner of the Year, KPBS Woman of the Year and Development Volunteer of the Year by National Society of Fund Raising Executives (NSFRE). She is also co-winner, with Donald Shiley, of the UCSD Distinguished Service Medal, 1998 Human Unity Award from the National Conference for Community and Justice, Philanthropists of the Year by NSFRE and the USD Presidents Award.

AWARDS/HONORS

Sydney Brenner was named the co-recipient of the 2002 March of Dimes Prize in Developmental Biology. The prize is awarded each year to outstanding scientists who have made exceptional findings in the field of birth defects prevention. Brenner was honored for his “tremendously influential” body of work that has helped revolutionize and open up new fields of study in molecular biology and genetics. Brenner also was named the first recipient of the Dan David Prize, an international prize awarded to people or institutions whose innovative and interdisciplinary work has an impact on one of three time periods. He was awarded this honor for his impact on the future.

Joseph R. Ecker was named a co-recipient of Kumbo Science International Award. He was cited for his leadership in completing the sequence for the first plant genome, Arabidopsis.

Fred H. Gage was named the co-recipient of the 2001 Award for Medical Research in Alzheimer’s Disease. Gage was honored for “pioneering achievements” that have led to a new understanding of the development of nerve tissue in adults and the potential use of neural stem cells to reverse the effects of neurodegenerative diseases, such as Alzheimer’s. Gage also was named the Vi and John Adler Professor in the Laboratory of Genetics and was elected to the Institute of Medicine, a branch of the National Academy of Sciences.

New Salk Logo Unveiled

The identity initiative that will become part of the strategic communications plan for the upcoming capital campaign was approved by the Salk Institute Board of Trustees during its New York meeting in April. Both words and graphics, created by the Scott Thornley Group of Toronto, Canada, are designed to help Salk delineate core messages that will establish in the public’s mind the importance of the Institute’s research and mission.

The initiative was undertaken with the guidance of the Institute’s marketing and communications committee, consisting of representatives from faculty, staff and leadership. “Where Cures Begin,” the Institute’s public message, conveys that the treatments, devices and cures known to medicine — today and in the future — have their origins in the kind of basic research done by our scientists. It’s a message we want the public to readily recognize and understand as inherent to the Salk Institute.

The logo is a simple and stylized version of our original Louis Kahn-designed architecture, which over the years has received international acclaim from architects and others. We’ll be using this new mark on Institute stationery, cards, invitations, publications and other related material.
Stephen F. Heinemann was elected to the Institute of Medicine, a branch of the National Academy of Sciences.

Tony Hunter received the Keio Medical Sciences Prize for his fundamental research into the molecular basis for cellular growth and cell cycle regulation. The award is given each year to a researcher or researchers “whose achievement is creative and distinguished, and has contributed to the advancement of life sciences related to medicine.” Hunter also was invited to present a talk during the Nobel Jubilee Symposium. To be invited to speak on such an occasion is a special honor, reflecting the high esteem in which Hunter is held by his peers.

Jan Karlseder has been named a V Foundation Scholar, awarded by The V Foundation for Cancer Research. The V Foundation, founded by ESPN and former college basketball coach Jim Valvano, is a charitable organization dedicated to saving lives by helping to find a cure for cancer. More specifically, The V Foundation seeks out promising young scientists from the finest research facilities across the country who need early developmental, critical-stage grant support.

John H. Reynolds was named a McKnight Neuroscience Scholar, given to young neuroscientists in the early stages of their research careers. Reynolds also was awarded the Fred Rentschler Chair, which supports young faculty members establishing their labs at the Institute. And he was selected to receive an Alfred P. Sloan Research Fellowship.

Charles F. Stevens was named The Vincent J. Coates Chair, given to support research in “molecular neurobiology aimed at elucidating the chemistry of the brain.”

An endowed lecture at Salk has been created in the name of Marguerite Vogt. Vogt, who turned 89 years of age, was named among 33 “R&D Stars to Watch” in the December 2001/January 2002 Industry Week magazine.

Detlef Weigel received the Charles Albert Shull Award from the American Society of Plant Biologists. The prize is given in odd-numbered years to outstanding investigators in the field of plant physiology residing in North America under the age of 40.

John Henry Felix Honored

A dinner honoring retiring board member John Henry Felix was held at the Sky Club in the MetLife Building in New York City during the April board meeting. A trustee of the Institute since 1989, John Henry served in various capacities at the Institute, providing leadership and guidance as chairman emeritus, vice chairman and chairman of the executive committee, and chairman of the development committee. He continues in a leadership capacity for the Salk Institute International Council.

International Council

More than 40 attended the annual Salk Institute International Council Meeting, held in May at the Salk Institute. The distinguished International Council members, leaders in their respective endeavors, attended seminars by Salk faculty, toured the Salk Institute laboratories and enjoyed the hospitality of President and CEO Richard A. Murphy and his wife Elaine. Among others, Distinguished Professor Francis H.C. Crick, Professors Fred H. Gage and Inder M. Verma spoke on consciousness, stem cells and diabetes, respectively. Nobel laureate and Distinguished Professor Renato Dulbecco, along with Professor Suzanne Bourgeois, updated the council on advances in cancer.

The council has played a key role in attracting private support to the Institute since its formation 25 years ago. The members, who represent a wide range of interests, including business, law and the arts, have been highly successful in raising awareness of the Institute’s work throughout the world.
SALK IN THE NEWS

A front-page feature in the November 10 issue of The San Diego Union-Tribune discussed reasons why many consider San Diego a powerhouse in the neurosciences. Salk scientists quoted or mentioned in the article included Fred H. Gage, Stephen F. Heinemann, Francis H.C. Crick, Roger Guillemin, Charles F. Stevens and Terrence J. Sejnowski. Gage and Heinemann were recently elected to the Institute of Medicine, which was noted in the Oct. 16 issue of the San Diego Daily Transcript.

Ursula Bellugi's studies on Williams Syndrome, the oft-puzzling genetic disorder, were featured in Scientific American Frontiers with Alan Alda. The PBS broadcast aired nationwide Wednesday, November 14 and Sunday, November 18. Bellugi has been searching for the underlying neurobiological basis for this disorder, which leaves language, facial recognition and social skills remarkably well-preserved, in contrast to severe inadequacy in other cognitive aptitudes.

An article in the December 4 issue of the Los Angeles Times magazine on the Nobel Prize highlighted Salk's three current Nobelists — Francis H.C. Crick, Roger Guillemin and Ronald M. Evans.

Renato Dulbecco — in addition to several others previously associated with Salk, including David Baltimore and Robert Holley.

The sale and housing of Francis H.C. Crick's scientific papers in London and La Jolla garnered international attention in the London Daily Telegraph, London Times and The San Diego Union-Tribune, among others.

The deciphering of the genome of the puffer fish Fugu rubripes by an international research team brought recognition to Sydney Brenner, who more than a decade ago argued for sequencing this species' genome. Stories about the results were carried in The New York Times, CNN and Science News, among others.

Fred H. Gage's discovery about neurogenesis in the adult human brain was highlighted in the November 2 issue of Science in an article about "Neuroscience: Unraveling and Repairing the Human Brain." The article said that Gage's findings "remodeled a significant portion of the foundation of neuroscience. In fact, many neuroscientists considered the discovery of neurogenesis in adult humans to be the discovery of the decade, and perhaps beyond."

Suggestions that the lack of new brain cell growth might trigger depression, which sprung from Gage's research, were highlighted in an article in the National Post in Toronto. Other research conducted by Gage and Henriette van Praag, showing that running could spur growth of new brain cells, was covered in the November 25 issue of The Chicago Tribune.

The continuing saga of the aging brain and how exercise might stimulate the growth of new neurons, research conducted by Gage's lab, was featured in an article carried by the Los Angeles Times Syndicate and in separate items in Newsday and the Air Force Times. Gage's most recent study offering proof that newly born cells in the adult brain function just like any of their neighbors was reported in The San Diego Union-Tribune, Scientific American, Wired, Reuter's Healthcare, Investor's Business Daily and the La Jolla Light.

The debate over the merits and ethics of stem cell research resulted in a series of articles in the December 18 science section of The New York Times. In one article, Fred H. Gage — a pioneer in the field of neuronal stem cells — mentioned that the brain generates an estimated 2,000 new neurons a day, running the gamut from place and face recognition to sense of smell. Inder M. Verma was featured in the...
December issue of Scientific American. Verma was quoted as saying “there will be a ‘hue and cry’ for the federal government to fund studies of newly generated stem cells if animal studies using the currently available stem cell lines show promise.” Another controversy over congressional bills that would ban all human cloning, including therapeutic cloning, was discussed by Verma in an op-ed article in the April 19 issue of The San Diego Union-Tribune. Inder spelled out the differences between reproductive cloning and therapeutic cloning, saying that no scientist was in favor of the former, but that most all scientists and scientific organizations had endorsed therapeutic cloning.

Studies by Ronald M. Evans showing a link between Vitamin A and learning were carried nationally over ABC affiliates in several major cities throughout the country.

Another study, showing the relationship between running and brain function, was also carried on ABC affiliates. Henriette van Pragg was featured in these latter presentations.

And an article on the front page of the October 10 issue of the La Jolla Village News, featuring research by Carrolee Barlow, discussed how running may help slow the progression of neurodegenerative disorders.

A feature on the many factors that control memory, published in the November issue of the Southwest Airlines Spirit magazine, quoted Charles F. Stevens about the value of forgetfulness, simply because our brains can’t store everything we’ve learned throughout our lives. One estimate tells us a lifetime’s worth of memories amounts to roughly 500 times the information stored in the Library of Congress.

From France, a profile on Leslie E. Orgel appeared in the October issue of Science et Vie, and a history of Nobelists who contributed to cell biology breakthroughs, reported in the October issue of La Recherche Medicale, included a segment on Francis H. C. Crick.

The Chicago Tribune asked Terrence J. Sejnowski about new research suggesting that near-death images and other hallucinations involving geometric patterns are really there — on the inside of the brain. Peter Thomas, one of the University of Chicago scientists who conducted the work, involving mathematical models of the internal circuitry of the brain’s visual system, has since joined Sejnowski’s lab at Salk.

Other scientists in Sejnowski’s lab also have received recent media recognition. Scott Makeig, a senior scientist and lead author of a paper that appeared in the January 24 issue of Science, reported that the brain works in a far more dynamic fashion than previously thought. The results are opening new avenues to explore certain brain dysfunctions, including schizophrenia and autism.

A computational model of hovering behavior, developed by postdoc Martina Wicklein, was the subject of a feature in the February 5 issue of The San Diego Union-Tribune. Wicklein is developing models of the visual system of hawkmoths who, like hummingbirds, hover in front of flowers while imbibing nectar. Aside from acquiring a basic understanding of this behavior, such knowledge might be used one day by engineers to help improve highway safety, warning drivers of a potential crash or for “smart cruise-control systems.”

Salk Nobelist Renato Dulbecco’s contributions to the betterment of city life in San Diego were mentioned by columnist Neil Morgan in the January 23 issue of The San Diego Union-Tribune. Morgan noted that Dulbecco is the only laureate known to have trained five other Nobel Prize winners.

Sydney Brenner was profiled in the March 18 cover story of The Scientist that featured a series of articles by friends and colleagues to commemorate his 75th birthday. Called “one of the most inventive and influential scientists of his generation,” Brenner’s life in science was sketched out by such luminaries as Paul Berg, Roger Brent, Jonathan Hodgkin, Horace Judson, Jonathan Karn, Chris Tan and Philip Tobias, in addition to Salk’s Francis H.C. Crick and Leslie E. Orgel. An article in the same issue of The Scientist discussed the Fugu genome project and its relevance to understanding the human genome. Fugu, the formal name for pufferfish, offers a compact version of the human genome, packing essentially the same information into one-eighth the DNA. The idea to use Fugu DNA sequences to probe the human genome came from Brenner.

The probable link between the breast cancer drug Herceptin and cardiac failure, one of its common side effects, was identified by a team led by Kuo-Fen Lee and reported in the April 30 issue of the journal Nature Medicine. The results may also explain why a common combination drug regimen including Herceptin is particularly toxic.

Studies in Joanne Chory’s lab suggesting a future with genetically engineered grass that stayed short, reducing mowing time, was featured in an article carried over the Newhouse News Service and the Toronto Sunday Star.
Save the Date:
Symphony at Salk

Enjoy an evening of enchantment and music at the annual Symphony at Salk: A Concert Under the Stars. Reserve your seat early for this stunning event, to be held this year Saturday, August 24. The musical program will be performed by the San Diego Symphony, with baritone Kevin Deas and soprano Indira Mahajan. Preconcert tours and box suppers will be available. For reservations or further information contact us at (858) 453-4100, ext. 1200.